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Attorneys for Defendants
Sun Pharmaceutical Industries Ltd. and
Sun Pharmaceutical Advanced Research Centre

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

ALTANA PHARMA AG and WYETH, Plaintiffs, v. SUN PHARMACEUTICAL INDUSTRIES LTD. and SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE Defendants.	Civil Action No.: 05-3920 (JLL)

SUN PHARMACEUTICAL INDUSTRIES LTD. AND SUN PHARMACEUTICAL ADVANCED RESEARCH CENTRE'S ANSWER, AFFIRMATIVE DEFENSES, AND COUNTERCLAIMS

Defendants Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Advanced Research Centre (hereinafter collectively "Sun"), by their attorneys, for their Answer respond as follows:

THE PARTIES

1. Sun is without information sufficient to form a belief as to the truth or falsity of the allegations in ¶ 1 of the Complaint and therefore denies them.

2. Sun is without information sufficient to form a belief as to the truth or falsity of the allegations in ¶ 2 of the Complaint and therefore, denies them.

3. Paragraph 3 is not a factual or legal allegation and requires no response.

4. Admitted.

5. Admitted.

6. Admitted.

7. Paragraph 7 is not a factual or legal allegation and requires no response.

8. Admitted.

9. Sun admits that it markets pharmaceutical products in the United States, including in New Jersey. Sun denies ¶ 9 of the Complaint in all other respects.

10. Sun admits that it manufactures pharmaceutical products and bulk pharmaceuticals that are sold and used in the United States, including in New Jersey. Sun denies ¶ 10 of the Complaint in all other respects.

11. Admitted.

12. Upon information and belief, Sun admits that New Drug Application No. 20-988 was approved by the United States Food & Drug Administration for 40 mg per vial pharmaceutical preparation which includes the active ingredient pantoprazole sodium and that such preparation is prescribed for gastro-intestinal disorders associated with acid secretion. Upon information and belief, Sun admits that such tablets are co-promoted in the United States under the trade name "PROTONIX®." To the extent not admitted, Sun is without further information sufficient for a belief as to the truth or falsity of the remaining allegations found in ¶ 12 of the Complaint and, therefore denies them.

13. Sun admits that United States Patent No. 4,758,579 ("the '579 patent")

issued on July 19, 1988, and that it purports to disclose certain compounds allegedly useful for inhibiting gastric acid secretion. Sun is without information sufficient to form a belief as to the truth or falsity of the remaining allegations found in ¶ 13 of the Complaint and therefore denies them.

14. Sun is without sufficient information to form a belief as to the truth or falsity of the allegations found in ¶ 14 of the Complaint and, therefore, denies them.

15. Sun admits that a copy of the '579 patent was attached as Exhibit A to the Complaint.

16. Admitted.

17. Admitted.

18. Admitted.

19. Sun is without information sufficient to form a belief as to the truth or falsity of the allegations in ¶ 19 of the Complaint and therefore denies them.

20. Sun is without information sufficient to form a belief as to the truth or falsity of the allegations in ¶ 20 of the Complaint and therefore denies them.

21. Sun denies that it infringes any valid and enforceable claim of the '579 patent.

22. Denied.

23. Denied, except that Sun admits it was aware of the existence of the '579 patent.

24. Denied.

25. Denied.

26. Denied.

PRAYER FOR RELIEF

27. In response to Plaintiffs' prayer for relief in the Complaint:

a. Sun denies that Plaintiffs are entitled to the relief requested in ¶ 27(a) of the Prayer for Relief.

b. Sun denies that Plaintiffs are entitled to the relief requested in ¶ 27(b) of the Prayer for Relief.

c. Sun denies that Plaintiffs are entitled to the relief requested in ¶ 27(c) of the Prayer for Relief.

d. Sun denies that Plaintiffs are entitled to the relief requested in ¶ 27(d) of the Prayer for Relief.

e. Sun denies that Plaintiffs are entitled to the relief requested in 27(e) of the Prayer for Relief.

f. Sun denies that Plaintiffs are entitled to the relief requested in ¶ 27(f) of the Prayer for Relief.

AFFIRMATIVE DEFENSES

FIRST AFFIRMATIVE DEFENSE

28. Upon information and belief, the claims of the '579 patent are invalid, void and/or unenforceable for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, 111, 112, 116, 132, 135, and 256.

SECOND AFFIRMATIVE DEFENSE

29. Sun will not infringe any valid and enforceable claim of the '579 patent under 35 U.S.C. § 271.

THIRD AFFIRMATIVE DEFENSE

30. The claims of the '579 patent which purport to cover pantoprazole are invalid under the judicially created doctrine of obviousness type double patenting.

FOURTH AFFIRMATIVE DEFENSE

31. Plaintiffs fail to state a valid claim for willful infringement.

COUNTERCLAIMS

Sun, for its counterclaims against Plaintiffs, alleges as follows:

THE PARTIES

1. Sun Pharmaceutical Industries Ltd. ("Sun") is a public limited liability company incorporated and existing under the laws of the State of India, and has a principal place of business located at Acme Plaza, Andheri Kurla Road, Andheri (East), Mumbai 400059, Maharashtra, India.

2. Upon information and belief, Altana Pharma AG ("Altana") is a corporation incorporated and existing under the laws of Germany, having its principal place of business at

Byk-Gulden-Str. 2, 78467 Konstanz, Germany.

3. Upon information and belief, Wyeth is a Delaware corporation with its headquarters located at Five Giralda Farms, Madison, New Jersey 07940.

JURISDICTION

4. This is a declaratory judgment action under 28 U.S.C. §§ 2201 and 2202. The counterclaims arise under the patent laws of the United States, 35 U.S.C. § 1 *et seq.* and under the Food, Drug and Cosmetic Act of the United States, 21 U.S.C. § 355(j). Jurisdiction is proper under 28 U.S.C. §§ 1331, 1338(a), 2201, 2202, and 21 U.S.C. § 355(j).

5. Upon information and belief, Altana directly or indirectly sells various products and conducts business throughout the United States.

6. Upon information and belief, Wyeth directly or indirectly sells various products and conducts business throughout the United States.

FACTUAL BACKGROUND

7. Upon information and belief, Altana is currently the owner of the United States Letters Patent Nos. 4,758,579 ("the '579 patent"), which purports to claim pantoprazole sodium, and 6,780,881 (the '881 patent"), which purports to claim a process for the production of a freeze-dried preparation of pantoprazole and a pantoprazole injection. A copy of the '881 patent is attached as Exhibit A.

8. Upon information and belief, Wyeth Pharmaceuticals, Inc., a wholly-owned subsidiary of Wyeth, holds an approved New Drug Application from the FDA for pantoprazole sodium for injection. Upon information and belief, Altana and Wyeth co-promote pantoprazole sodium for injection under the trade name "PROTONIX® IV."

9. Sun has filed with the FDA ANDA No. 77-674 for approval to market a

pantoprazole sodium for injection in the United States.

10. Sun sent a notice letter related to ANDA No. 77-674 pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) to Wyeth and Altana on June 25, 2005, which notice letter, upon information and belief, was received by Altana in or about June 2005, and by Wyeth in or about June 2005, respectively. The notice letter informed Altana and Wyeth that Sun's ANDA No. 77-674 contains a certification that, in the opinion of Sun and to best of its knowledge, both the '579 patent and the '881 patent are not infringed, invalid, and/or unenforceable.

11. Pursuant to 21 U.S.C. § 355(j)(5)(C), Sun's Notice Letter included an Offer of Confidential Access to Sun's ANDA No. 77-674. Sun provided ANDA No. 77-674 to counsel for Altana and Wyeth under the terms of a Confidentiality Agreement.

12. On or about August 5, 2005, Altana and Wyeth filed or caused to be filed a Complaint for patent infringement which alleges that Sun's filing of ANDA No. 77-674 infringes the '579 patent. However, the Complaint contains no allegations of infringement of the '881 patent.

13. There is an actual, substantial, and continuing justifiable controversy between Sun and Defendants concerning the infringement, validity, and enforceability of the '579 patent and the '881 patent.

COUNT I

INVALIDITY OF THE '579 PATENT

14. The allegations of ¶¶ 1-13 of Sun's Counterclaims are repeated, realleged, and incorporated herein by reference.

15. Upon information and belief, the claims of the '579 patent are invalid, void and/or unenforceable for failure to comply with the statutory prerequisites of Title 35 of the

United States Code, including without limitation, one or more of §§ 101, 102, 103, 111, 112, 116, 132, 135, and 256.

16. The claims of the '579 patent are invalid under the judicially created doctrine of obviousness type double patenting.

COUNT II

NON-INFRINGEMENT OF THE '579 PATENT

17. The allegations of ¶¶ 1-13 of Sun's Counterclaims are repeated, realleged and incorporated herein by reference.

18. Sun will not infringe any valid and enforceable claim of the '579 patent under 35 U.S.C. § 271.

COUNT III

INVALIDITY OF THE '881 PATENT

19. The allegations of ¶¶ 1-13 of Sun's Counterclaims are repeated, realleged, and incorporated herein by reference.

20. Upon information and belief, the claims of the '881 patent are invalid, void and/or unenforceable for failure to comply with the statutory prerequisites of Title 35 of the United States Code, including without limitation, one or more of §§ 101, 102, 103, 111, 112, 116, 132, 135, and 256.

COUNT IV

NONINFRINGEMENT OF THE '881 PATENT

21. The allegations of ¶¶ 1-13 of Sun's Counterclaims are repeated, realleged and incorporated herein by reference.

22. Sun will not infringe any valid and enforceable claim of the '881 patent

under 35 U.S.C. § 271.

PRAYER FOR RELIEF

WHEREFORE, Sun prays that the Court enter:

A. A declaratory judgment that the '579 patent is invalid;

B. A declaratory judgment that Sun will not infringe any valid and enforceable claim of the '579 patent under 35 U.S.C. § 271;

C. A declaratory judgment that the '881 patent is invalid;

D. A declaratory judgment that Sun will not infringe any valid and enforceable claim of the '881 patent under 35 U.S.C. § 271;

E. An Order enjoining and restraining Altana and Wyeth and their officers, agents, servants, employees, attorneys, and those persons in active concert or participation with them from further charges of infringement or acts of enforcement based on the '579 patent and '881 patent against Sun, its actual and prospective customers, suppliers, clinical investigators, and anyone in privity with Sun; and

F. An Order awarding Sun such other further relief as the Court deems just and equitable.

Dated: September 21, 2005

PROSKAUER ROSE LLP

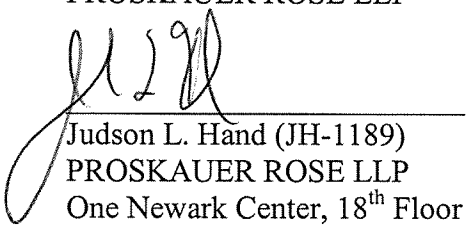

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EXHIBIT A

US006780881B2

(12) **United States Patent**
Linder et al.

(10) **Patent No.: US 6,780,881 B2**
(45) **Date of Patent: Aug. 24, 2004**

(54) **FREEZE-DRIED PANTOPRAZOLE PREPARATION AND PANTOPRAZOLE INJECTION**

(75) Inventors: **Rudolf Linder**, Constance (DE); **Rango Dietrich**, Constance (DE)

(73) Assignee: **Altana Pharma AG**, Constance (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/195,062**

(22) Filed: **Jul. 15, 2002**

(65) **Prior Publication Data**

US 2003/0003058 A1 Jan. 2, 2003

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/EP01/13296, filed on Nov. 17, 2001.

(30) **Foreign Application Priority Data**

Nov. 22, 2000 (EP) 00125569

(51) **Int. Cl.**[7] **A61K 31/44**; A61K 31/41; A61K 9/19; A61K 9/14; C07D 235/04

(52) **U.S. Cl.** **514/338**; 514/925; 514/926; 514/927; 514/359; 514/360; 424/46; 548/304.4

(58) **Field of Search** 514/338, 935, 514/926, 927, 359, 360; 424/46; 548/304.4

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,589,491 A 12/1996 Nakanishi et al.

FOREIGN PATENT DOCUMENTS

CN	1 235 018	11/1999
DE	43 24 014	1/1995
WO	WO 94/02141	2/1994
WO	WO 99/18959	4/1999

OTHER PUBLICATIONS

Dietrich, Rango, DE 4324014, Jan. 19, 1995, Preparation of a lyophilized, water–reconstitutable formulation of Pantoprazol Sodium Sesquihydrate, Abstract.*

BASF–Pharma UK, Section 3—Summary of Product Characteristics "Protium i.v. pantoprazole sodium lyophile". Jan. 2000.

Kibbe, A.H., "Handbook of Pharmaceutical Excipients". Pharmaceutical Press, pp. 191–194, 649, (2000).

Physician's Desk Reference, PDR Entry for Protonix I.V. (Wyeth–Ayerst), vol. 58 (2004), pp. 3480–3483.

* cited by examiner

Primary Examiner—Frederick Krass
Assistant Examiner—Clinton Ostrup
(74) *Attorney, Agent, or Firm*—Nath & Associates PLLC; Todd L. Juneau; Sheldon M. McGee

(57) **ABSTRACT**

Lyophilized pantoprazole preparations which are obtainable by freeze-drying of an aqueous solution of pantoprazole, ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate are disclosed. The preparations have advantageous properties when reconstituted for injection.

24 Claims, No Drawings

FREEZE-DRIED PANTOPRAZOLE PREPARATION AND PANTOPRAZOLE INJECTION

This application is a Continuation-In-Part of International Patent Application No. PCT/EP01/13296 with an international filing date of 17 Nov. 2001, the entire contents of the application which is hereby incorporated in its entirety.

TECHNICAL FIELD

The present invention relates to the field of pharmaceutical technology and describes freeze-dried 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl) methylsulfinyl]-1H-benzimidazole preparations and a 5-difluoromethoxy-2-[(3,4dimethoxy-2-pyridinyl) methylsulfinyl]-1H-benzimidazole injection. Further-more the invention also relates to a process for the production of freeze-dried 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole and a 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl) methylsulfinyl]-1H-benzimidazole injection.

PRIOR ART

WO94/02141 describes an injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5. It is mentioned that said injection does not cause hemolysis and causes less local irritation.

DE 43 24 014 describes the preparation of a lyophilisate of pantoprazole-sodium sesquihydrate in the presence of sucrose as an auxiliary at production temperatures of −25 to −30° C. It is disclosed that the lyophilisate is of improved storage stability and can be stored at room temperature for at least 18 months and is easily reconstituted in liquid form in suitable doses for use.

CN 1235018 describes a freeze-dried injection powder of pantoprazole sodium containing no crystallised water with pH value of 9–12.5, which is composed of pantoprazole sodium, freeze-dried powder supporting agent, metal ion complexing agent and pH regulator.

WO99/18959 describes aqueous pharmaceutical compositions which are chemically and physically stable for intravenous injection which comprise anti-ulcerative compound and glycine as stabilizer in carrier.

DESCRIPTION OF INVENTION

Reconstitution of lyophilised pharmaceutical compounds with carrier solutions for application may lead to the formation of visible and/or subvisible particles in the solution. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use should be essentially free from particles that can be observed on visual inspection and for patient safety it is also desirable to have a low number of subvisible particles. USP (United States Pharmacopoeia) 24 describes physical tests performed for the purpose of enumerating subvisible extraneous particles within specific size ranges and also defines particulate matters limits set forth for the test being applied for large-volume Injections for single-dose infusion and small-volume injections (U.S. Pat. No. 24, <788>Particulate Matter in Injections).

Surprisingly it has now been found that by freeze drying of an aqueous solution of pantoprazole, ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate a lyophilisate is obtained having significantly lower number of subvisible particles after reconstitution with a solvent compared to lyophilisates of the state of the art. The lyophilisate according to the invention is very stabile and is easily reconstituted with suitable solvents. In particular the pantoprazole injection according to the invention has less than 130, preferably less than 120 subvisible particles/per vial, the particles having a size equal to or greater as 10 μm, the number of particles determined according to U.S. Pat. No. 24 (<788>Particle Matter in Injections) by light obscuration particle test count.

5-Difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl) methylsulfinyl]-1H-benzimidazole (INN; pantoprazole, in connection with the invention also referred to as pantoprazole) is known from EP-A-0 166 287. Pantoprazole is a chiral compound. In connection with the invention the term pantoprazole also includes the pure enantiomers of pantoprazole and their mixtures in any mixing ratio. (S)-pantoprazole [(−)-pantoprazole] may be mentioned by way of example. Pantoprazole is present here as such or preferably in the form of it's salt with a base. Examples of salts with a base which may be mentioned are sodium, potassium, magnesium and calcium salts. Pantoprazole and/or a salt thereof may contain various amounts of solvent when isolated in crystalline form. In connection with the invention pantoprazole also refers to all solvates and in particular to hydrates of 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole and salts thereof. Such a hydrate of the salt of pantoprazole with a base is disclosed, for example, in WO91/19710. Expediently pantoprazole refers to pantoprazole sodium sesquihydrate (=pantoprazole sodium×1.5H_2O) and pantoprazole magnesium dihydrate.

According to the invention the pantoprazole solution used in the freeze drying process can be obtained by addition of ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate to an aqueous solvent. Suitable salts of ethylenediamine tetraacetic acid which may be mentioned in connection with the invention by way of example are ethylenediamine tetraacetic acid disodium salt, ethylenediamine tetraacetic acid calcium disodium salt ethylenedlamine tetraacetic acid trisodium salt and ethylenedlamine tetraacetic acid tetrasodium salt. The proportion by weight of ethylenediamine tetraacetic acid and/or a suitable salt thereof, based on the amount of pantoprazole used is from 0.05 to 25% preferably from 0.25 to 12.5% or particular preferred from 1 to 5%. The aqueous solvent preferentially is water for injection. Subsequently pantoprazole is added to the solution and dissolved by stirring. It is preferred to have a solution wherein the proportion of weight (m/m) of pantoprazole is 0.5 to 10%, particularly preferred 1 to 6%. In a further preferred embodiment of the invention the pH of the solution used in the freeze drying process is 8 or above 8. Particularly preferred the pH of said solution is in the range from 10 to 13, more preferred the pH of the solution is in the range from 10.5 to 11.5 and particularly more preferred the pH is in the range from 10.75 to 11.25. Exemplary pH values of said solution, which are to be emphasized are 10.75, 10.8, 10.85, 10.9, 10.95, 11, 11.05, 11.1, 11.15, 11.2 and 11.25. Then this solution is filtered for sterilization and charged in vials. The solution is then freeze dried by a method known per se.

A pantoprazole injection according to the invention can be produced by dissolving the lyophilized product thus obtained in a suitable solvent for example physiological

saline, aqueous solution of 5% glucose, or distilled water for injection. Preferably the pantoprazole injection according to the invention is used in the form of intravenous injection.

The lyophilised product and pantoprazole injection according to the invention preferably contain pantoprazole in the dose customary for the treatment of the respective disease. The lyophilised product and pantoprazole injection according to the invention can be employed for the treatment and prevention of all the diseases which are regarded as treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, the lyophilised product and pantoprazole injection according to the invention can be employed in the treatment of stomach disorders. The lyophilized products in particular contain between 5 and 150 mg, preferably between 5 and 60 mg, of pantoprazole. Examples which may be mentioned are lyophilized products or injections which contain 10, 20, 40, 50 or 96 mg of pantoprazole. The administration of the daily dose (e.g. 40 mg of active compound) can be carried out, for example, in the form of an individual dose or by means of a number of doses of the administration forms according to the invention (e.g. 2 times 20 mg of active compound). The concentration of pantoprazole in the injection according to the invention may vary depending upon the administration route and generally ranges in a proportion of 0.05–10 mg/ml, preferably 0.1 to 5 mg/ml on a free compound basis. For example for bolus administration 20 to 120 mg of lyophilized product according to the invention can be reconstituted with 10 ml physiological saline.

The production of the lyophilized product and pantoprazole injection is described by way of example below. The following examples illustrate the invention in greater detail, without restricting it.

EXAMPLES

Production of a Lyophilized Pantoprazole Preparation

Example 1

Under nitrogen atmosphere, 0.276 g Ethylenediamine tetraacetic acid disodium salt and 6.7 g sodium hydroxide (1 N aqueous solution) are added to 480 g water for injection of 4° C. to 8° C. 12.47 g pantoprazole sodium sesquihydrate is added while stirring to give a clear solution. The weight of the solution is adjusted to 500 g by addition of water for injection. The pH of the solution is 11.76. The solution is filtered through a 0.2 μm membrane filter and filled in glass vials (1.81 g by vial). Filled vials are semi-stoppered and put into a freeze-dryer (GT4 Edwards/Kniese or GT8 Amsco) for lyophilisation. The vials are cooled to −45° C., then the temperature is raised to −20 to −5° C. under vacuum (0.1 to 0.5 mbar) for drying. After finishing main drying the temperature is raised to 30° C., the vacuum is adjusted to 0.01 mbar and drying is continued for an additional 3 hours. An off-white lyophilized product is obtained which is easily reconstituted with physiological saline to give a clear solution.

Example 1a

Under nitrogen atmosphere, 0.276 g Ethylenediamine tetraacetic acid disodium salt and 1.66 ml sodium hydroxide solution (1N aqueous solution) are added to 480 g water for injection of 4° C. to 8° C. 12.47 g pantoprazole sodium sesquihydrate is added while stirring to give a clear solution. The weight of the solution is adjusted to 500 g by addition of water for injection. The pH of the solution is 11.76. The solution is filtered through a 0.2 μm membrane filter and filled in glass vials (1.81 g by vial). Filled vials are semi-stoppered and put into a freeze-dryer (GT4 Edwards/Kniese or GT8 Amsco) for lyophilisation. The vials are cooled to −45° C. then the temperature is raised to −20 to −5° C. under vacuum (0.1 to 0.5 mbar) for drying. After finishing main drying the temperature is raised to 30° C., the vacuum is adjusted to 0.01 mbar and drying is continued for an additional 3 hours. An off-white lyophilized product is obtained which is easily reconstituted with physiological saline to give a clear solution.

Comparative Examples

Example 2

Under nitrogen atmosphere, 12.47 g pantoprazole sodium sesquihydrate is added to 480 g water for injection of 4° C. to 8° C. while stirring to give a clear solution. The volume of the solution is adjusted to 500 g by addition of water for injection. The pH of the solution is 10.85. The solution is filtered through a 0.2μm membrane filter and filled in glass vials (1.81 g by vial). Filled vials are semi-stoppered and put into a freeze-dryer (GT4 Edwards/Kniese or GT8 Amsco) for lyophilisation. The vials are cooled to −45° C., then the temperature is raised to −20 to −5° C. under vacuum (0.1 to 0.5 mbar) for drying. After finishing main drying the temperature is raised to 30° C., the vacuum is adjusted to 0.01 mbar and drying is continued for an additional 3 hours. An off-white lyophilized product is obtained.

Example 3

Under nitrogen atmosphere, 2.45 g sodium hydroxide (1N aqueous solution) is added to 480 g water for injection of 4° C. to 8° C. 12.47 g pantoprazole sodium sesquihydrate is added while stirring to give a clear solution. The weight of the solution is adjusted to 500 g by addition of water for injection. The pH of the solution is 12.02. The solution is filtered through a 0.2 μm membrane filter and filled in glass vials (1.81 g by vial). Filled vials are semi-stoppered and put into a freeze-dryer (GT4 Edwards/Kniese or GT8 Amsco) for lyophilisation. The vials are cooled to −45° C., then the temperature is raised to −20 to −5° C. under vacuum (0.1 to 0.5 mbar) for drying. After finishing main drying the temperature is raised to 30° C., the vacuum is adjusted to 0.01 mbar and drying is continued for an additional 3 hours. An off-white lyophilized product is obtained.

Example 4

Under nitrogen atmosphere, 0.05 g Ethylenediamine tetraacetic acid disodium salt is added to 480 g water for injection of 4° C. to 8° C. 12.47 g pantoprazole sodium sesquihydrate is added while stirring to give a clear solution. The weight of the solution is adjusted to 500 g by addition of water for injection. The pH of the solution is 10.2. The solution is filtered through a 0.2 μm membrane filter and filled in glass vials (1.81 g by vial). Filled vials are semi-stoppered and put into a freeze-dryer (GT4 Edwards/Kniese or GT8 Amsco) for lyophilisation. The vials are cooled to −45° C., then the temperature is raised to −20 to −5° C. under vacuum (0.1 to 0.5 mbar) for drying. After finishing main drying the temperature is raised to 30° C. the vacuum is adjusted to 0.01 mbar and drying is continued for an additional 3 hours. An off-white lyophilized product is obtained.

Light Obscuration Particle Test Count

Particulate matter/per vial in solutions constituted from the lyophilized products obtained according to Examples 1

to 4 were determined according to USP 24 (<788>Particulate Matter in Injections) by light obscuration particle test count.

The number of extraneous particles per vial having a size equal to or greater as 10 μm detected are summarized in Table 1. As may be evident from table 1, the number of subvisible particles per vial (equal to or greater as 10 μm) in solutions constituted from products obtained according to the invention (EXAMPLE 1) is lower than for products obtained by methods which differ from the present invention (EXAMPLES 2 to 4).

TABLE 1

EXAMPLE 1 (Product obtained by freeze drying of Pantoprazole sodium sesquihydrate, sodium hydroxide and ethylenediamine tetraacetic acid disodium salt) particles/ per vial > = 10 μm	EXAMPLE 2 (Product obtained by freeze drying of Pantoprazole sodium sesquihydrate) particles/ per vial > = 10 μm	EXAMPLE 3 (Product obtained by freeze drying of Pantoprazole sodium sesquihydrate and sodium hydroxide) particles/ per vial > = 10 μm	EXAMPLE 4 (Product obtained by freeze drying of Pantoprazole sodium sesquihydrate and ethylene-diamine tetraacetic acid disodium salt) particles/ per vial > = 10 μm
109	458	144	211

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.

What is claimed is:

1. Process for the production of a freeze-dried preparation comprising 5-difluoromethoxy-2-[(3,4-di-methoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (pantoprazole), a salt thereof, a solvate of pantoprazole or a salt thereof, comprising freeze-drying of an aqueous solution of pantoprazole, a salt thereof, a solvate of pantoprazole or a salt thereof, ethylenedlamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate, wherein upon dissolution in an aqueous solvent, the preparation has less than 130 subvisible particles per vial, the particles having a size equal to or greater than 10 μm, wherein the number of particles is determined according to USP 24 by light obscuration particle test count.

2. Process according to claim 1, wherein the solution is prepared by the following steps:

a. dissolving ethylenediamine tetraacetic acid and/or a suitable salt thereof in water,

b. adjusting the pH of the solution to 8 or above 8 by adding sodium hydroxide and/or sodium carbonate to the solution, and

c. adding pantoprazole, a salt thereof, a solvate of pantoprazole or a salt thereof, to the solution.

3. Process according to claim 1, wherein the ethylenedlamine tetraacetic acid and/or suitable salt thereof is present in an amount from about 0.05 to about 25% by weight, based on the amount of pantoprazole present.

4. Process according to claim 1, wherein the pantoprazole used in the step of freeze-drying is pantoprazole sodium sesquihydrate.

5. Process according to claim 1, wherein the aqueous solution has a pH of between about 10 to about 13.

6. Process according to claim 1, wherein the aqueous solution has a pH of between about 10.5 to about 11.5.

7. Process according to claim 1, wherein the aqueous solution has a pH of between about 10.75 to about 11.25.

8. Process according to claim 1, wherein the aqueous solution has a pH value that is selected from the group consisting of 10.75, 10.8, 10.85, 10.9, 10.95, 11, 11.05, 11.1, 11.15, 11.2, and 11.25.

9. Process according to claim 1, wherein ethylenediamine tetraacetic acid and/or suitable salt thereof is present in an amount from about 0.25 to about 12.5% by weight, based on the amount of pantoprazole present.

10. Process according to claim 1, wherein the ethylene-diamine tetraacetic acid and/or suitable salt thereof is present in an amount from about 1 to about 5% by weight, based on the amount of pantoprazole present.

11. Process according to claim 1, wherein the preparation has less than 120 subvisible particles per vial upon dissolution in an aqueous solvent.

12. Process according to claim 1, wherein the pantoprazole used in the step of freeze-drying is pantoprazole sodium.

13. Process according to claim 1, wherein the pantoprazole used in th step of freeze-drying is pantoprazole magnesium.

14. Process according to claim 1, wherein the pantoprazole used in the step of freeze-drying is pantoprazole magnesium dihydrate.

15. Lyophilized pantoprazole preparation obtainable by a process according to claim 1.

16. Injection kit comprising a lyophilized pantoprazole preparation according to claim 15 and an aqueous solvent for bolus administration.

17. Pantoprazole injection for bolus administration obtainable by reconstitution of the pantoprazole preparation according to claim 15 in an aqueous solvent.

18. Pantoprazole injection according to claim 17, wherein the solvent is physiological saline.

19. Pantoprazole injection having less than 130 subvisible particles per vial, the particles having a site equal to or greater than 10 μm, wherein the number of particles is determined according to USP 24 by light obscuration particle test count.

20. Pantoprazole injection according to claim 19, having less than 120 subvisible particles per vial.

21. Pantoprazole injection according to claim 19, wherein the pantoprazole is present therein is obtained from pantoprazole sodium sesquihydrate.

22. Pantoprazole injection according to claim 19, wherein the pantoprazole is present therein is obtained from pantoprazole sodium.

23. Pantoprazole injection according to claim 19, wherein the pantoprazole is present therein is obtained from pantoprazole magnesium.

24. Pantoprazole injection according to claim 19, wherein the pantoprazole is present therein is obtained from pantoprazole magnesium dihydrate.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,780,881 B2
DATED : August 24, 2004
INVENTOR(S) : Linder et al.

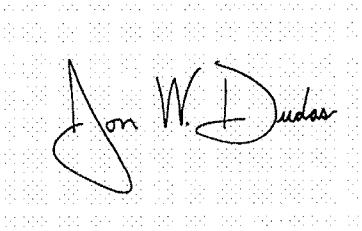
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 41, "ethylenedlamine" should read -- ethylenediamine --.
Line 57, "ethylenedlamine" should read -- ethylenediamine --.

Column 6,
Line 27, "used in th step" should read -- used in the step --.
Line 43, "having a site equal" should read -- having a size equal --.
Lines 50, 53, 56 and 59, "the pantoprazole is present" should read -- the pantoprazole present --.

Signed and Sealed this

Fourth Day of January, 2005



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Director of the United States Patent and Trademark Office